REMARKS

Claims 1 to 120 were previously canceled. Claims 122 to 123, and 127 to 130 are canceled herein. Claims 121 and 124 to 126 are currently pending for the Examiner's consideration.

Applicant respectfully requests favorable consideration of the pending claims.

Claim Objections

Claims 122 to 123, and 127 to 130 were objected to under 37 CFR 1.75 as being substantial duplicates of claims 121 and 123 to 126. Without acceding to the Examiner's objection, and purely in the interests of advancing prosecution of the instant claims, Applicant has canceled claims 122 to 123, and 127 to 130. Applicant respectfully asserts the objection to these claims is therefore moot and requests withdrawal thereof.

Rejections under 35 U.S.C. § 103

Claims 121 to 130 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Tang et al. (WO 01/60814) and Shenoy et al. (WO 01/37820) for the reasons set forth on pages 3-9 of the Office Action. Rejected claims 122, 123, and 127 to 130 have been canceled. With regard to currently pending claims 121 and 124-126, Applicant respectfully traverses the rejection.

The objective technical problem to be solved for the present invention is to provide a pharmaceutically acceptable, stable formulation of the specified indolinone malate which can be readily formed into an oral capsule or tablet, and which does not provide processing difficulty during the formulation process, particularly during a capsule filling process.

It has been surprisingly found that the claimed invention provides a pharmaceutically acceptable, stable formulation of the specified indolinone malate that does not suffer from flow or adhesion problems during the capsule filling process. In addition, the claimed invention exhibits pharmaceutically acceptable dissolution and stability properties. As such, given these desirable properties, it is one of the commercial formulations for the drug sunitinib malate(SUTENT) (n.b. sunitinib is the generic name of the indolinone compound of the claimed invention).

Nonobviousness

Reference D12 ("Pharmaceutical Capsules", Second Edition, Podczeck and Jones, Pharmaceutical Press, 2004, pages 101-104) is an extract from a standard textbook on pharmaceutical capsule technology. In the Introduction to Chapter 5 on page 101 it is stated:

> *"Factors that require consideration during the development of two-piece hard capsules are the capsule size in relationship to the required fill weight and dose of the drug, the filling method, the powder, granule or pellet properties, the bioavailability of the active ingredient and the stability of the formulation."*

Also, in the right-hand column on page 102 it is suggested that:

> *"**Minor flow problems** might occur, which can be removed by addition of an optimal amount of a lubricant."* (emphasis added)

The powder adhesion problem is then discussed and then it is stated:

> *"The addition of optimised quantities of lubricants and glidants **might** also be sufficient to solve the problem"* (emphasis added) and then magnesium stearate/silicon dioxide and magnesium stearate/talcum powder are recommended as possible solutions.

On page 103 in the section on "Stickiness" it is stated:

> *"**Stickiness of powders to all metal parts of capsule filling machinery is a serious problem, which is often difficult to solve.** It causes a large variability in fill weight and in the extreme case the machine will cease to function after prolonged running time"* (emphasis added)

then

> *"When using dosator nozzle filling machinery, stickiness caused by adhesion can only be overcome by modification of the formulation.".*

Therefore, Reference **D12** teaches that many factors must be considered in designing a formulation and process for preparing capsules. It is then suggested that minor flow problems and powder adhesion might be solved by optimised addition of a lubricant and/or glidant. However, stickiness to metal parts of capsule machinery is a serious problem that may only be overcome in dosators by modifying the formulation. Thus, it is clear that when powder adhesion occurs it is a difficult

problem to solve and while addition of a lubricant and/or glidant might solve the problem, it also may not. Further, any change in a formulation may affect the other significant properties of the formulation rendering it unsuitable for drug development.

In summary, trying to use, or attempting to optimize the amount of, a lubricant or glidant <u>does not lead to an expectation of success in solving the present objective technical problem</u>.

Reference D13 ("Pharmaceutics, The Science of Dosage Form Design", Second Edition, Aulton, Churchill Livingstone, 2002, pages 456-460) is an extract from a standard textbook on pharmaceutical dosage form technology. In the "Formulation" section on page 456, it is stated:

> *"All formulations for filling into capsules have to meet the same basic requirements:*
>
> 1. ***They must be capable of being filled uniformly to give a stable product.***
> 2. *They must release their active contents in a form that is available for absorption by the patient.*
> 3. *They must comply with the requirements of the Pharmacopoeiae and regulatory authorities, e.g.* ***dissolution tests.****"* (emphasis added)

Then, in the "Powder formulation" section, it is stated:

> *"The majority of products for filling into capsules are formulated as powders. These are typically mixtures of the active ingredient together with a combination of different types of excipients… The ones selected depend on several factors:*
> - ***The properties of the active drug***
> - ***Its dose, solubility, particle size and shape***
> - *The size of the capsule to be used."* (emphasis added)

On page 458, it is then stated:

> "*Some excipients, such as* ***lubricants*** *and glidants, are added to formulations to improve their filling properties,* ***and these can sometime have an effect on release***." (emphasis added)

There then follows an extensive discussion of a number of examples where the presence or used amount of magnesium stearate was shown to have a marked effect on release, dissolution rate and/or cohesiveness.

Finally, on page 459 it is stated:

> *"The formulator has to produce a product that complies with 3 formulation goals. Sometimes these are contradictory: for example, extra hydrophobic lubricant is required for filling machine performance,* ***which could interfere with release***" (emphasis added)

Hence this reference teaches that many factors need consideration in designing a formulation and process for preparing capsules and that satisfactory release, absorption and dissolution are very important. It is then firmly stated that addition of a lubricant and/or glidant can have an effect on release and this is evidenced to have occurred in practice using several literature examples. It is thus clear that when powder adhesion occurs, it is a difficult problem to solve and while addition of a lubricant and/or glidant might solve the problem, it may also not. Further, any change in a formulation may affect the other significant properties of the formulation, such as release or dissolution, rendering it unsuitable for drug development. In summary, trying to use, or attempting to optimize the amount of, a lubricant or glidant does not lead to an expectation of success in solving the present objective technical problem.

Further, **Reference D14** ("Encyclopedia of Pharmaceutical Technology", Second Edition, Marcel Dekker Inc., Swarbrick and Boylan, 2002, pages 310-314) is an extract from a standard textbook on pharmaceutical technology. In the chapter discussing "Hard Capsules" it is stated in the "Formulation" section on page 310:

> *"****Powder formulations for capsule-filling must have good flow properties, be nonadhesive****, and be cohesive enough to form plugs at low compression forces****. In addition, they must be stable and release the active ingredient in the desired manner.****"* (emphasis added)

On page 311 it is continued:

> *"****Another hindrance to obtaining good fill-weight uniformity on machines is adhesion of material to moving parts, particularly to dose-measuring devices****."* (emphasis added)

Pages 312-313 then state:

> ***" In preparing a formulation, a formulator needs to take into account the physicochemical properties of the active ingredient, the nature and type of excipients required, and the filling process*** *(10).* ***The properties of the active drug that are most significant are its aqueous solubility*** *and particle size……...****Certain excipients added to formulations to improve filling-machine performance can have an adverse effect on release because they are hydrophobic in nature. This is true of lubricants, which are added to formulations to prevent adhesion and to improve flow. The most used excipient in capsule formulations in both the United States and Europe is magnesium stearate (52, 53). This is hydrophobic, and there are many reports in the literature concerning its adverse effect on dissolution rates. However, the relationship between the concentration of magnesium stearate and release rate is not quite as simple as for tablets, in which an increase in amount brings a proportional decrease in release. The reason for this is the very different nature of tablets and capsules.*** *A tablet is compressed using high forces to form a solid compact of relatively low porosity and must be if it is to survive subsequent handling. A hard capsule product, on the other hand, contains a powder mass of high porosity, which may or may not have been compressed into a plug, and is contained within the shell that can withstand handling.* ***Magnesium stearate functions as a lubricant when it is dispersed on the surfaces of other particles. At this site, it also reduces the cohesion of particles, and thus as its concentration increases, the powder mass will become weaker. Several workers have shown that an increase in magnesium stearate concentration has increased dissolution rates: small particles are made less cohesive (Fig. 7) (54), and powder plugs are weakened, thus breaking apart more readily when the capsule shell has dissolved (Fig. 8) (55). If the level in the formulation is not optimized, then there is a possibility that during the filling operation, the magnesium stearate will be gradually dispersed to a greater extent, resulting in changes in dissolution or weight uniformity (10, 56).*** *"* (emphasis added)

Finally, it is stated on page 314:

> *"Product formulations must meet a number of goals. They must be able to be filled by machines to give a uniform, stable product. They must release the active ingredients in a manner to give the desired therapeutic effects. They must comply with the regulatory and compendial specifications.* ***The excipients used in formulations often have properties that aid compliance with one aspect but, at the same time, can have a negative effect on another goal. The relationship among the factors is complex****."* (emphasis added)

This reference (**D14**) teaches that many factors need consideration in designing a formulation and process for preparing capsules and that good flow properties, nonadhesion, stability and active ingredient release profile are very important. It is then stated that adhesion can be a serious issue and that the addition of excipients, including lubricants, can have an adverse effect on release profile. It is clearly stated that there are "*many reports in the literature*" of the adverse effect of the addition of magnesium stearate on dissolution rates and then a detailed analysis of the problems and issues created by using magnesium stearate in capsule formulations follows. It is clear that complex problems can occur when using magnesium stearate in capsule formulations which can be very difficult to solve particularly since drug release and other formulation properties may be affected. As noted previously, trying to use, or attempting to optimize the amount of, a lubricant does not lead to an expectation of success in solving the present objective technical problem.

Following this teaching in the art, the disclosures of the cited references are better understood in context.

First, **D01** (WO01/37820), describes formulations of indolinones which are ionizable as free acids or free bases. The free base of the indolinone specified for the claimed invention is listed as Example 80 in Table 1 on page 39, and on page 158. However, the L-malate salt is not specifically described. Although **D01** is concerned generally with obtaining pharmaceutically acceptable formulations of said indolinones, it is not specifically directed at solving the present objective technical problem which is to provide a pharmaceutically acceptable, stable formulation of the specified indolinone malate which can be readily formed into an oral capsule or tablet and which does not provide processing difficulty during the formulation process. In addition, **D01** does not teach or suggest the same or a similar formulation to that of the claimed invention, let alone that the problem of adhesion during the capsule filling process can be solved using such a specified type of formulation. Accordingly, Applicant respectfully submits that the claimed invention is not *prima facie* obvious in view of the **D01** teaching.

Second, **D04** (WO01/60814) discloses pharmaceutically acceptable formulations of novel indolinones. The free base of the indolinone specified for the claimed invention is listed as Example 80 in Table 1 on page 38. The L-malate salt is described in claim 49. Although **D01** is concerned generally with obtaining pharmaceutically acceptable formulations of said indolinones, it is not specifically directed at solving the present objective technical problem which is to provide a pharmaceutically acceptable, stable formulation of the specified indolinone malate which can be readily formed into an oral capsule or tablet and which does not provide processing difficulty during the formulation process. In addition, **D04** does not teach or suggest the same or a similar formulation to that of the claimed invention, let alone that the problem of adhesion during the capsule filling process can be solved using such a specified type of formulation. Accordingly, the claimed invention is again not *prima facie* obvious in view of this second (**D04**) teaching.

Further Evidence of Nonobviousness

As further evidence for nonobviousness, comparative data are adduced as follows.

The present application discusses in paragraphs 0207-0208 a comparative example in which capsule formulations of the claimed invention and a similar formulation containing 75% w/w of the specified indolinone are prepared. This 75% w/w formulation was used as the initial drug batch for clinical studies during the development of sunitinib. It is stated that during capsule production using the 75% w/w formulation:

"...excessive sticking problems were observed during the capsule filling process. The sticking problems occurred in the hopper, filling heads and other moving parts of the capsule filling machine. The sticking problems necessitated halting the capsule filling process several times to clean machine parts". (paragraph 0207)

However, it is then stated that during capsule production using the claimed 40% w/w formulation:

"The improved formulation did not exhibit the sticking problems observed with the 75% w/w formulation". (paragraph 0208)

The attached Technical report (**D11)** provides the detailed technical evidence for these results. In summary, **D11** shows that:

- The 75% w/w formulation (that was used as the initial drug batch for clinical studies during the development of sunitinib) causes severe granulate adhesion problems during the capsule filling process meaning that the process had to be frequently stopped to clean the machine parts before the filling process could re-commence. This formulation is thus not acceptable for drug development.
- However, the claimed 40% w/w commercial sunitinib formulation surprisingly does not cause granulate adhesion problems during the capsule filling process.
- The 75% w/w formulation had acceptable dissolution and dissolution stability properties that allowed it to be used as the initial drug batch for clinical studies during the development of sunitinib.
- The claimed 40% w/w commercial sunitinib formulation has similarly acceptable pharmaceutically acceptable dissolution and dissolution stability properties as also seen for the 75% w/w formulation.

Summary

None of the prior art references cited, alone or in combination, hints or suggests that the present objective technical problem could be solved using the claimed invention and as such it is not prima facie obvious. When a specific formulation is devised, it is not possible to easily predict its properties, let alone predict its granulate adhesion, stability and dissolution characteristics, for example. Applicant respectfully submits that the comparative Example in the present application, and the enclosed Technical report **D11**, convincingly show that the claimed invention unexpectedly solves the granulate adhesion problem encountered with the initial development formulation used for clinical studies, and it has, for example, pharmaceutically acceptable dissolution and stability properties.

Conclusion

Applicant believes all claims are now in condition for allowance. Should there be any issues that have not been addressed to the Examiner's satisfaction, Applicant invites the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, including the fee for any required extension of time (for which Applicant hereby petitions), please charge such fees to Deposit Account No. 161445.

Respectfully submitted,

Date: **October 19, 2010**

/Keith D. Hutchinson/
Keith D. Hutchinson
Attorney For Applicant
Registration No. 43,687

Pfizer Inc
Legal Division – Intellectual Property
10555 Science Center Drive
San Diego, California 92121
Phone: (858) 526-4608
Fax: (858) 678-8233

Attachment A

Technical Report D11 and Annexes 1-5 are attached hereto.